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EXAMINER	
RAMIREZ, DELIA M	
ART UNIT	**PAPER NUMBER**
1652	

DATE MAILED: 05/04/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/856,679	HILLMAN ET AL.	
	Examiner	Art Unit	
	Delia M. Ramirez	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 February 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *21-30,32 and 34-44* is/are pending in the application.

4a) Of the above claim(s) *21-23 and 34-44* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *24-30 and 32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

Claims 21-30, 32, 34-44 are pending.

Applicant's amendment of claims 21, 27-30, 32, cancellation of claims 31, 45, in a communication filed on 2/19/2004 is acknowledged.

Applicant's submission on 2/19/2004 of two declarations under 37 CFR 1.132 by John Rockett and Vishwanath Iyer, several publications by Rockett and coworkers, several publications by Iyer and coworkers, a publication by Schena et al., a publication by Lashkari et al., a publication by Anderson et al., publications and several patents by Ekins et al., a WIPO document by Rosenberg et al., a WIPO document by Seilhamer et al., a WIPO document by Shalon et al., a WIPO document by Martin et al., a US patent by Ashby et al., a publication by Heller et al., a Genetic Engineering News article, a New York Times article, a Today's News web article, and an Agilent Technologies web article, are acknowledged.

Applicants argue that claims 34-36, 43-44 should be co-examined together with the claims directed to the elected invention as they are methods of use of the elected polynucleotides. Applicant's request has been considered however in view of the fact that the elected product has not been found allowable, the restriction requirement between the claimed polynucleotides and the methods of use is maintained. When the product is found allowable, withdrawn process claims that depend from or otherwise include all the limitations of the allowable product claim will be rejoined in accordance with the provisions of MPEP § 821.04.

Applicants request the withdrawal of the lack of unity of invention previously applied between claims drawn to polynucleotides and claims drawn to the polypeptides encoded by the polynucleotides, i.e. claims 21-23 and 37-42 due to the cancellation of claim 33 and the amendment of claims 21 and 32 which no longer recite a fragment. Applicant's request has been fully considered but is not deemed persuasive for the following reasons. First, if lack of unity were to be withdrawn between claims drawn

to the polynucleotide and the polypeptide, due to the amendment of claims 21 and 32 as well as the cancellation of claim 33, there is still lack of unity between the polypeptides and the methods of use of said polypeptide. Applicants are reminded that the elected group already contains one method of use and 37 CFR 1.475(d) does not provide for the inclusion of multiple methods of use within the main invention. Claims 38-42 are directed to methods of use of the polypeptide and will not be rejoined. Furthermore, even taking into consideration the amendment of claims 21, 32 and the cancellation of claim 33, claims drawn to the polypeptide (claims 21-23 and 37) lack unity of invention with the elected claims according to PCT Rule 13.2 as unity of invention only exists when the shared same or corresponding technical feature is a contribution over the prior art. The inventions of claims 21-30, 32, and 37 do not relate to a single general inventive concept because thy lack the same or corresponding special technical feature. The technical feature of claims 24-30 and 32 is to be a polynucleotide that encodes the polypeptide of SEQ ID NO: 2 which is shown by Muzny et al. (already discussed in a previous Office Action mailed on 10/17/2003) to lack novelty or inventive step as this reference discloses a polynucleotide which encodes the polypeptide of SEQ ID NO: 2 and does not make it a contribution over the prior art.

This application contains claims 21-23, 34-45 drawn to an invention non-elected with traverse in Paper No. 8. A complete reply to the final rejection must include cancellation of non-elected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Claim Objections

1. Claims 24-26 remain objected to because they depend upon non-elected claims, i.e. claims 21-23. It is suggested that the claims be rewritten to incorporate those limitations recited in the non-elected claims. For examination purposes, the claims will be interpreted as having the limitations recited in the non-elected claims. Appropriate correction is required.

Claim Rejections - 35 USC § 101

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

3. Claims 24-30 and 32 remain rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a substantial and specific asserted utility or a well established utility.

4. Claims 24-30 and 32 also remain rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

5. These rejections has been discussed at length in Paper No. 10, mailed on 10/17/2003.

6. Applicants argue that the invention at issue is a polynucleotide corresponding to a cAMP-regulated guanine nucleotide exchange factor expressed in reproductive, nervous and cardiovascular tissues in humans. According to Applicants, the invention has numerous uses in toxicology testing, drug development, and diagnosis of disease, none of which requiring knowledge of the biological function of the polypeptide encoded by the claimed polynucleotides. Applicants submit declarations under 37 CFR 1.132 declarations by Dr. John Rockett and Dr. Vishwanath Iyer, attachments to these declarations, and 10 scientific references which applicants submit were published before or shortly after the November 23, 1998 priority date of the instant application. Applicants submit that these declarations and references have been submitted to demonstrate that it was well-established in the art that (1) polynucleotides can be used as hybridization probes to determine the presence, absence and the amount of expression of a particular gene, (2) polynucleotides having sufficient length generate a signal that is specific to the corresponding gene, (3) expression analysis is useful in drug discovery, toxicology, and phenotypic characterization of cell types, (4) each additional probe useful in expression analysis provides an additional gene-specific signal thus providing a more comprehensive, robust, statistically more

significant, and more useful expression pattern, (5) biologists recognize the utility of more comprehensive results and want each newly identified expressed gene to be included in their analysis and in their microarrays, (6) nucleic acid microarrays provide data analogous to that provided by other techniques but at substantially increased throughput, (7) adding additional gene-specific probes to the signaling component of a microarray increases the detection range and versatility of this research tool, (8) industrial suppliers strive to improve their product by adding each newly identified expressed gene to the microarrays they sell, (9) it is not required to know the biological function of a gene for measurement of their expression in drug discovery, toxicology, or molecular phenotyping experiments, (10) failure of a probe to detect changes in expression or failure of a probe to detect a transcript in a expression analysis experiment does not deprive the probe of its usefulness. According to Applicants, these declarations and scientific reference demonstrate that one of skill in the art can achieve beneficial results from the claimed polynucleotides without knowing the biological function of the polypeptide encoded by them and that gene expression monitoring does not require disclosure of biological function.

7. Applicant's arguments have been fully considered but are not deemed persuasive to overcome the rejection previously applied. For the record, it is noted that this is the first time Applicants assert that the claimed polynucleotides encode a cAMP-regulated guanine nucleotide exchange factor expressed in reproductive, nervous and cardiovascular tissues in humans. As indicated in previous Office Action Paper No. 10, mailed on 10/17/2003, while there is an assertion in the specification indicating that the polypeptide of SEQ ID NO: 2 (encoded by the polynucleotide of SEQ ID NO: 31) is a GTPase associated protein, the specification does not assert that the polypeptide of SEQ ID NO: 2 is a cAMP-regulated guanine nucleotide exchange factor. The only reference in the specification regarding a cAMP-regulated guanine nucleotide exchange factor is in reference to a rat cAMP-regulated guanine nucleotide exchange factor which was found to be the closest structural homolog of the polypeptide of SEQ ID NO: 2. Even if one assumes that there is an assertion in the specification indicating that the polypeptide of

SEQ ID NO: 2 encodes a cAMP-regulated guanine nucleotide exchange factor, as indicated previously the invention lacks a specific and substantial or well established utility as nothing is known about its specific targets, the biological processes/pathways associated with this exchange factor, or diseases/conditions associated with the expression or lack thereof, of a polynucleotide encoding the polypeptide of SEQ ID NO: 2. Furthermore, this utility is not substantial since additional research would be required to identify its biological function such that one could reasonably confirm a real world context of use.

Applicant's submission of the declarations by Rockett and Iyer, attachments and references has been fully considered. However, the Examiner disagrees with Applicant's contention that knowledge of biological function is not required for the claimed polynucleotides to have patentable utility as probes or in gene expression analysis. The Examiner acknowledges that (1) polynucleotides can be used as hybridization probes to determine the presence, absence and the amount of expression of a particular gene, (2) the longer a polynucleotide probe is, the more specific it is, (3) expression analysis is useful in drug discovery, toxicology, and phenotypic characterization of cell types, (4) additional probes useful in expression analysis provide expression patterns having higher resolution (5) nucleic acid microarrays provide data analogous to that provided by other techniques but at substantially increased throughput, (6) adding additional gene-specific probes to the signaling component of a microarray increases the detection range and versatility of this research tool, and (7) it is not required to know the biological function of a gene for measuring its expression. However, use of the claimed polynucleotides as hybridization probes or in microarrays to determine expression patterns is not specific for those polynucleotides as any expressed polynucleotide can be used as a hybridization probe or in a microarray to determine expression patterns. In fact, both declarations indicate that this use is not specific to the claimed polynucleotides. Rockett in page 2 of the declaration indicates that for patterns of gene expression, thousands of genes are monitored (lines 1-4) to obtain a pattern of gene expression. Iyer in pages 3-4 of the declaration clearly

states that any new gene probe added to a microarray increases the resolution of the expression pattern. In both declarations, it is clear that in the applications described by Rockett and Iyer, the identity of the polynucleotides used in expression profiling is not required, thus any expressed polynucleotide can be used in their expression profiling studies.

The Examiner is not disputing that (1) any expressed polynucleotide can be used as a probe or in gene expression analysis, or (2) gene expression analysis is used in toxicology, phenotype characterization of cell types, or in drug discovery. However for these uses to be specific and substantial as they relate to the claimed polynucleotides, one of skill in the art would require some knowledge or guidance as to the biological function of the polypeptide encoded by the claimed polynucleotide such that one could effectively use the information gathered in tracking the expression patterns of said polynucleotides. The reduction or increase in expression of a polynucleotide is meaningless unless one can link changes in expression with some biological function, disease, or condition. For example, if one were to use the claimed polynucleotides in assays which would lead to the discovery of drugs for a specific condition, such as an assay which uses a DNA microarray to evaluate expression patterns of the claimed polynucleotides upon exposure to a test compound, one needs to know the expression of the claimed polynucleotides is associated with the diseases for which a therapeutic drug is sought. If this information is unknown, one of skill in the art would have to carry out further experimentation to determine which are the conditions (i.e. diseases) and/or biological functions associated with the claimed polynucleotides and how to interpret the results obtained from the gene expression analysis. Since no information has been provided regarding how the expression of the claimed polynucleotides is associated with any disease/biological process or how to interpret results obtained from gene expression analysis, this utility is not substantial. Similarly, for the claimed polynucleotide to have a specific and substantial use in phenotype characterization, one would require some knowledge as to which specific cell types would express the claimed polynucleotides. To determine which cell types can be distinguished by the

claimed polynucleotides would also require further experimentation. Thus, this utility is also not substantial.

While Applicants assert that the claimed polynucleotides can be used in diagnosis of disease without knowing the biological function of the polypeptide encoded by said polynucleotides, it is noted that the specification does not provide any clue as to which specific diseases can be diagnosed with the claimed polynucleotides nor does it provide any clue as to the levels of expression which are indicative of disease. The Examiner agrees that knowing the exact biological function of a polypeptide is not required for diagnosis of a disease if there is some evidence of a correlation between the polypeptide or its corresponding polynucleotide and disease. For example, Shattuck-Eidens et al. (JAMA 278(15):1242-1250, 1997) discloses mutant alleles of the BRCA1 gene that predispose a patient to develop breast and ovarian cancers. While there is no disclosure of the function of the mutant BRCA1 genes or their gene products, there is clear evidence that there is a correlation between the presence of these mutant alleles of BRCA1 and susceptibility to develop breast cancer. In contrast, the specification in the instant case is completely silent in regard to a correlation between the claimed polynucleotides and any specific disease. Since the instant specification does not disclose an specific and substantial "real world" use for the polynucleotide of SEQ ID NO: 31 or a polynucleotide encoding the polypeptide of SEQ ID NO: 2, then the claimed invention as disclosed does not meet the requirements of 35 U.S.C. §101 as being useful.

Claim Rejections - 35 USC § 112, First Paragraph

8. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

9. Claims 24, 26, 28-30, and 32 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that

the inventor(s), at the time the application was filed, had possession of the claimed invention. This rejection has been discussed at length in Paper No. 10, mailed on 10/17/2003.

10. Applicants argue that the specification provides an adequate written description of the recited variants of SEQ ID NO: 2 since the specification discloses the structure of the polypeptide of SEQ ID NO: 2 and the variants recited are defined in terms of SEQ ID NO: 2 such that the precise chemical structure of every variant within the scope of the claims can be discerned. Furthermore, Applicants argue that it would be routine for one of ordinary skill in the art to recognize whether a naturally occurring polypeptide is a variant of the polypeptide of SEQ ID NO: 2 as recited in the claims. Applicants further refer to *Fiers v. Revel* and *University of California v. Eli Lilly and Co.* in support of the argument that while in those cases written description was found lacking since the genus of compounds claimed were defined on the basis of functional characteristics, in Applicant's case the genus of nucleic acids claimed is defined solely on structural features. Applicants submit that the claimed genus is not highly variant and refer to Brenner et al. (Proc. Natl. Acad. Sci USA 95:6073-6078, 1998). Specifically, Applicants argue that Brenner et al. have determined that (1) 30% identity is a reliable threshold for establishing evolutionary homology between two sequences aligned over at least 150 residues, and (2) a 40% or more identity over at least 70 residues is reliable in signifying homology between proteins. Since the genus recited require that the polypeptides be at least 90% sequence identical, which is much higher than the 30% threshold of Brenner et al., applicants conclude that the variation recited, i.e. 90%, is not high. Applicants also submit that much has happened since the priority date claimed for the instant application and that the state of the art is further advanced than at the time of the Lilly and Fiers applications.

11. Applicant's arguments have been fully considered but are not deemed persuasive to overcome the rejection. The claims as amended are directed to (1) a genus of nucleic acids encoding naturally occurring polypeptides of any function having at least 90% sequence identity to the polypeptide of SEQ ID NO: 2, (2) a genus of naturally occurring nucleic acids encoding polypeptides of any function, wherein

said nucleic acids have at least 90% sequence identity to the polynucleotide of SEQ ID NO: 1, and (3) a method to recombinantly produce the proteins encoded by the genus of (1). While the specification does not specifically define the intended meaning of the term "naturally-occurring", one of skill in the art would interpret such term as meaning "as found in nature", which is the case with allelic variants. Thus, the claimed genera will encompass allelic variants of the gene encoding the polypeptide of SEQ ID NO: 2, unknown genes encoding homologs of the polypeptide of SEQ ID NO: 2 and their corresponding allelic variants. The specification defines an "allelic variant" (page 8) as an alternative form of the gene which may result in at least one mutation in the nucleic acid sequence. Alleles may result in altered mRNAs or polypeptides whose structure or function may or may not be altered. This definition does not provide any specific information about the structure of naturally occurring alleles of the gene encoding the polypeptide of SEQ ID NO: 2 (i.e. where are the regions within which mutations are likely to occur), nor does it provide any information as to the functional effects of the mutation. The specification is completely silent as to the mutational sites that exist in nature and there is no description of how the structure of the polynucleotide of SEQ ID NO: 31 relates to the structure of any naturally-occurring variant as claimed. In the case of alleles, there is no indication in the art that would suggest that the structure and function of one provides guidance to the structure and function of others. Therefore, it is unclear as to how one of skill in the art can reasonably conclude that the disclosure of the structure of the polypeptide of SEQ ID NO: 2 or the structure of the polynucleotide of SEQ ID NO: 31 is sufficient to adequately describe any naturally occurring variant as asserted by Applicants.

While the Examiner agrees that the claimed polynucleotides must share a common structural feature, and acknowledges the findings in *Fiers v. Revel* and *Univ. of California v. Eli Lily and Co.*, it is noted that claimed genus is one of substantial variation in function. Variation in functional features was not an issue in *Fiers* or *Lilly* because in those cases the disputed claims recited a functional limitation. In the instant case, there is no functional limitation. The written description requirement for a claimed genus

may be satisfied through sufficient description of a representative number of species sufficient to show applicants were in possession of the claimed genus. A representative number of species means that the species that are adequately described are representative of the entire genus. In the instant case, one cannot reasonably conclude that the single species disclosed, i.e. SEQ ID NO: 31, is representative of the claimed genus in view of the fact that the claimed polynucleotides can potentially have many functions which are undisclosed.

In regard to the teachings of Brenner et al. (Proc. Natl. Acad. Sci USA 95:6073-6078, 1998), it is noted that the instant reference could not be found in the case. However, the Examiner obtained a copy and has considered the reference.

While the Examiner agrees that the scope of a genus of polynucleotides claimed is smaller than that of a genus of polynucleotides encoding proteins having 30% sequence identity over 150 amino acids of the polypeptide of SEQ ID NO: 2, as indicated by the teachings of Bork, Van de Loo et al., and Broun et al., high structural homology does not always result in functional homology. In addition to the references already cited which indicate the unpredictability of assigning function based on structural homology, Brenner (TIG 15:132-133, 1999) teaches that empirical laboratory evidence is essential to know the accuracy of functional assignment (page 132, left column, second paragraph). Furthermore, Witkowski et al. (Biochemistry 38:11643-11650, 1999) teaches that one amino acid substitution transforms a β-ketoacyl synthase into a malonyl decarboxylase and completely eliminates β-ketoacyl synthase activity. The art clearly teaches that a genus of polynucleotides as the one claimed can potentially encode proteins of different function which can not be inferred by structural homology alone. Since the specification provides no guidance as to which structural elements in the polypeptide of SEQ ID NO: 2 are characteristic of GTPase associated proteins, one of skill in the art cannot reasonably conclude that the genus of polynucleotides claimed will only encode GTPase associated proteins.

In regard to the teachings of Brenner et al. (Proc. Natl. Acad. Sci. USA 95:6073-6078, 1998), it is noted that the purpose of the study of Brenner et al. was to identify distant evolutionary structural homology using sequence comparison algorithms. Nowhere does Brenner et al. teach that the results obtained can be extrapolated for use in predicting functional homology of any unknown protein. Furthermore, Brenner et al. discloses that the comparisons "have been assessed using proteins whose relationships are known reliably from their [three dimensional] structures and functions, as described in the SCOP database" (page 6073, Abstract). The proteins within the SCOP database have been fully characterized, meaning their functions have been characterized by empirical laboratory experiments and their 3D structures have been generated. Therefore, the results disclosed in Brenner et al. are applicable only for identifying evolutionary structural homology and not functional homology, as Appellants assert. Even if one assumes that the results of Brenner et al. could be applied for functional annotation of uncharacterized proteins of any function, Brenner et al. teaches that the 30% identity for alignments of at least 150 residues threshold is applicable only to the protein database used (PDB90D-B) and that the 40% identity over at least 70 residues threshold is a reasonable threshold for a database of the size and composition of that of PDB90D-B. See page 6076, right column, lines 20-26. Nowhere in the instant reference, is there a statement indicating that these thresholds can be used to predict the function of any unknown protein. Therefore, in view of the teachings of the art as presented by the Examiner, as well as Appellants, it is unclear as to how one of skill in the art can reliably predict the function of any polypeptide with a 30% sequence identity over 150 residues or 40% identity over 70 residues threshold based solely on sequence homology as asserted by Appellants. Thus, one cannot reasonably conclude that a genus of polynucleotides as that claimed is not potentially a functionally variable genus.

While it is agreed that much has happened in the area of recombinant DNA technology from the time the applications involved in Fiers and Lilly, the state of the art after 1999 as extensively discussed

above, teaches the unpredictability of determining function based on structural homology without any teaching or suggestion as to how structure correlates with function.

12. Even if specific and substantial utility or well established utility is found for the polynucleotide of SEQ ID NO: 31 or a polynucleotide encoding the polypeptide of SEQ ID NO: 2, the following rejection applies. Claims 24, 26, 28-30, and 32 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a polynucleotide encoding the polypeptide of SEQ ID NO: 2, does not reasonably provide enablement for polynucleotides of any function (1) encoding polypeptides having at least 90% structural identity to SEQ ID NO: 2, or (2) having at least 90% structural identity to SEQ ID NO: 31. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. This rejection has been discussed at length in Paper No. 10, mailed on 10/17/2003.

13. Applicants argue that the claims recite the term "naturally-occurring" and given the information provided by the structures of SEQ ID NO: 2 and SEQ ID NO: 31, one of skill in the art would be able to routinely obtain "naturally-occurring" polypeptides which are at least 90% sequence identical to the polypeptide of SEQ ID NO: 2. Applicants submit that one of skill in the art can use PCR to identify those relevant polynucleotides found in nature and that all that is required is to screen a cDNA library or use appropriate PCR conditions. Applicants also submit that one can make fragments of naturally occurring polynucleotides at least 90% sequence identical to the polynucleotide of SEQ ID NO: 31, and use these fragments as probes. It is Applicant's opinion that the identity of those residues in the polypeptide of SEQ ID NO: 2 which are tolerant of modification and/or which are conserved has no bearing on the ability of one of skill in the art to screen cDNA libraries of use appropriate PCR conditions to identify relevant polynucleotides without undue experimentation. According to Applicants, it is irrelevant whether any of the claimed polynucleotides encode a polypeptide having a biological function

since it is not required for a polynucleotide to encode a functional polypeptide for one of skill in the art to be able to use that polynucleotide without undue experimentation. Applicants refer to *In re Marzocchi* and assert that the Office has failed to provide any reasons why one would doubt that the guidance provided by the specification would enable one of skill in the art to make and use the claimed invention.

14. The Examiner disagrees with Applicant's contention that the claimed invention is enabled for the full scope of the claims. While screening cDNA libraries and isolating polynucleotides using probes or PCR techniques is well known and widely used in the art, the Examiner disagrees that the specification discloses how to isolate "naturally occurring" polynucleotides as claimed. As indicated above and reiterated herein, the term "naturally occurring" encompasses allelic variants. However, the specification is completely silent regarding the structures of naturally occurring alleles of the gene encoding the polypeptide of SEQ ID NO: 2 (i.e. where are the regions within which mutations are likely to occur), or any information as to the functional effects of the mutations. There is no information as to (1) the mutational sites that exist in nature, or (2) how the structure of the polynucleotide of SEQ ID NO: 31 relates to the structure of any naturally-occurring variant as claimed. In the case of alleles, there is no indication in the art that would suggest that the structure and function of one provides guidance to the structure and function of others. Thus, it is unclear as to how one of skill in the art can make fragments of a naturally occurring polynucleotide having at least 90% sequence identity to the polynucleotide of SEQ ID NO: 31 and use this fragments to probe other polynucleotides if the specification fails to disclose (1) how to make naturally occurring polynucleotides or (2) which are the structural elements in the only polynucleotide disclosed (SEQ ID NO: 31) common to other naturally occurring polynucleotides as claimed.

Furthermore, while it is agreed that polynucleotides encoding non-functional variants of the polypeptide of SEQ ID NO: 2 or the polynucleotide of SEQ ID NO: 31 can be used to detect other polynucleotides such as the polynucleotide of SEQ ID NO: 31, fragments of the polynucleotide of SEQ

ID NO: 31 can also be used to detect a polynucleotide encoding the polypeptide of SEQ ID NO: 2. This use is not specific to the claimed genus of polynucleotides. It is noted that even if the polynucleotide of SEQ ID NO: 31 and polynucleotides encoding the polypeptide of SEQ ID NO: 2 are found to have patentable utility, the genus of variants claimed must also be shown to have a patentable use under the "how to use" requirement of 35 USC 112, first paragraph. As such, the claimed genus of polynucleotides must have a specific and substantial or well-established utility. However, Applicant's asserted use for the claimed genus of polynucleotides as hybridization probes is not specific.

Regarding the lack of reasons as to why one would doubt the guidance presented in the specification, it is noted that the Examiner previously indicated in Paper No. 10, mailed on 10/17/2003 the reasons why it would require undue experimentation to enable the full scope of the claims and cited references which teach the unpredictability of the art regarding determining a function for the claimed polynucleotides. It was clearly stated that in view of the teachings of the specification and the unpredictability of the art, as evidenced by Bork, Broun et al., and Van de Loo et al., regarding accurate annotation of function based solely on structural homology, one of skill in the art would have to go through the burden of undue experimentation to determine which of the claimed polynucleotides encode proteins having the same function as that of the polypeptide of SEQ ID NO: 2 and how to use those polynucleotides which encode proteins of unknown function. Furthermore, the Examiner has cited the teachings of Brenner and Witkowski et al. as additional evidence showing the unpredictability of assigning function based on structural homology alone. Therefore, contrary to Applicant's assertions, the Examiner has presented reasons and evidence as to why it would require undue experimentation to enable the full scope of the claims.

Claim Rejections - 35 USC § 102

15. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

16. Claims 24-26 remain rejected under 35 U.S.C. 102(a) as being anticipated by Muzny et al. (GenBank accession number AC004241 GI3108007, May 2, 1998). This rejection has been discussed at length in Paper No. 10, mailed on 10/17/2003.

17. Applicants argue that Muzny et al. is not pertinent to the claimed polynucleotides as the claimed polynucleotides are "full length" and that the genomic DNA of Muzny et al. contains numerous intervening sequences between the coding segments. According to Applicants, the present claims define polynucleotides which are "full length" and as such these "full length" polynucleotides do not contain intervening sequences.

18. Applicant's arguments have been fully considered but are not deemed persuasive to overcome the rejection. While it is agreed that the polynucleotide of SEQ ID NO: 31 is a full length polynucleotide in that it contains an open reading frame without introns (i.e. intervening non-coding fragments), it is noted that the claims do not recite any limitation regarding the presence or absence of introns. The claims are directed to polynucleotides encoding the polypeptide of SEQ ID NO: 2 or a structural homolog of the polypeptide of SEQ ID NO: 2. As such, the genomic DNA of Muzny et al. will anticipate said claims as the genomic DNA of Muzny et al. while containing introns, encodes the entire polypeptide of SEQ ID NO: 2.

Conclusion

19. No claim is in condition for allowance.

20. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

21. Certain papers related to this application may be submitted to Art Unit 1652 by facsimile transmission. The FAX number is (703) 872-9306. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If Applicant submits a paper by FAX, the original copy should be retained by Applicant or Applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

22. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PMR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

23. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Delia M. Ramirez whose telephone number is (571) 272-0938. The examiner can normally be reached on Monday-Friday from 8:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ponnathapura Achutamurthy can be reached on (571) 272-0928. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1234.

Delia M. Ramirez, Ph.D.
Patent Examiner
Art Unit 1652

DR
April 27, 2004

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